REMARKS

Claims 8-12, 19-31, 34-51 and 55-74 are pending in the application. Claims 29-31, 37-45 and 59-66 are withdrawn from consideration as being drawn to non-elected inventions. Claims 73 and 74 are allowed. Claims 8-12, 19, 28, 34, 46, 47, 50, and 55-58 have been amended to better clarify what Applicants regard as the invention. Support for the amendments can be found throughout the specification, in particular on page 3, lines 1-3; on page 10, lines 3-6; on page 11, lines 15-19; on page 41, lines 13-20; in the Examples on pages 41-52 and in the claims as originally filed. No new matter has been added by way of this amendment. Thus, as a result of the foregoing amendment, claims 8-12, 19-28, 34-36, 46-51, 55-58 and 67-74 remain pending. Reconsideration of this application is respectfully requested.

Rejections under 35 U.S.C. §112

Claims 8-12, 19-28, 34-36, 46-51, 55-58 and 67-72 are rejected under 35 USC §112, first paragraph for lack of enablement. More particularly, the Examiner alleges that while the the specification is enabled for "increasing neural expression of eNCAM, MAP II, beta-tubulin, nestin, NF or NF-PO4 in the bone marrow or neural cells ", "promoting growth or differentiation of neural precursor cells" or "treating spinal cord injury by administering bone marrow from N-[4-[(4-fluorophenyl) sulfonyl]-acetamide-treated animal to a site of injury in animal", it does not reasonably provide enablement for "promoting neural cell growth or differentiation", "promoting recovery of cells expressing neuronal progenitor cell markers after injury to the neuronal cells", "promoting neural cell growth or differentiation of neural cells" and "treating injury to neuronal cells", with the administration of compounds of formula (II). Furthermore, the Examiner alleges that the specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to practice the invention commensurate in scope with these claims.

The Examiner notes that the invention relates to promoting neural tissue regeneration or neural expression. Moreover, the specification defines neural tissue as "all tissue endogenous to the nervous system" (page 13, lines 10-12 and lines 22-26), neural expression as the expression of any proteins indicative of neural tissue growth or neural tissue cell differentiation from progenitor cells (page 13, lines 13-18), and neural progenitor cells as "any cell that can differentiate into a neural tissue cell, or be induced to differentiate into a

neural tissue cell, including neural precursor cells, whether directly or through intermediate cell stages" (page 14, lines 103). As the specific embodiments of the invention, the Examiner notes that the instant specification discloses in-vitro studies performed to test the activity of N-[4[(4-fluorophenyl) sulfonyl]-acetamide in increasing neural expression of eNCAM, MAP II, beta-tubulin, nestin, NF, and NF-PO4 (Examples 1 and 2) and in-vitro studies done to test the activity of N-[4-[(4- fluorophenyl) sulfonyl]phenyl]-acetamide in increasing the growth of neurons or astrocytes (Example 4). The instant specification also discloses that animals (Fischer F344 female rats) treated with bone marrow cells from N-[4-[(4- fluorophenyl) sulfonyl]phenyl]-acetamide treated donor animals demonstrate a decrease in cavity size at the confusion injury site, in vivo study (Example 3).

However, the Examiner alleges that the specification does not provide sufficient guidance for the skilled artisan to ascertain (i) which proteins indicative of neural tissue growth or neural tissue cell differentiation from progenitor cells other than the disclosed proteins, *eg*. eNCAM, MAP II, beta-tubulin, nestin, NF, and NF-PO4, and (ii) which neural tissues, neural precursor cells or progenitor cells other than bone marrow cells would be enabled in this invention in animals or human. Furthermore, the Examiner alleges that the specification does not provide sufficient guidance for the skilled artisan how to ascertain that (iii) the growth of neurons or astrocytes by the administration of N-[4-[(4- fluorophenyl) sulfonyl]phenyl]-acetamide *in vitro* would lead to the improvement of the functional recovery of neurons, and (iv) provide the effective treatment of complex neurodegenerative diseases or conditions that may have unrelated manifestation *in vivo*, without undue amount of experimentation.

The Examiner further alleges that the instant invention relates to methods of promoting neural cell growth or differentiation (claims 8-12, 34-36, 67-68); a method for promoting recovery of cells expressing neuronal progenitor cell markers after injury to the neuronal cells (claims 19-28); a method for treating injury to neuronal cells (claims 46-51, 55-56); a method for promoting growth and differentiation of neural precursor cells (claims 57-58), wherein methods requires the administration of compounds of formula II. More specifically, claims 34-36 and 57-58 are directed to a transplantation method.

The Examiner alleges that with the exception of "method of increasing neural expression of eNCAM, MAP II, beta-tubulin, nestin, NF, and NF-PO4", "promoting growth or differentiation of neural precursor cells" or "treating spinal cord injury by administering bone marrow cells from animals treated with the compounds of the invention to a site of

injury in animal", the skilled artisan cannot envision that (a) the administration of N-[4-[(4-fluorophenyl) sulfonyl]phenyl]-acetamide is capable of increasing the expression of other known neural proteins (e.g., vimentin, Sox2, Ki-67, GD2 ganglioside, MAP2ab, NeuN. FMRP, Tau, GFAP, dublecortin, CD133, CD44, CD81, CD90, CD29, NumA and etc...), and (b) promoting regeneration of diverse neural tissues, neural precursor cells, progenitor cells or tissue of neural origin (e.g., schwann cells, stem cells, oligodendrocytes, etc...) in animals or human; and (c) the administration of N-[4-[(4- fluorophenyl) sulfonyl]phenyl]-acetamide, without neutralizing the nerve-growth inhibitory properties of various proteins in the CNS environment, is capable of providing the desired effects of the claimed invention, particularly claims 8-12, 19-28, 46-56 and 67-72 where no transplantation method is required, in animals or human.

Moreover, the Examiner alleges that the breadth of the instant claims encompasses promotion of neural cells (e.g., stem cells, progenitor cells, neurons, glial cells, astrocytes, oligodendrites, etc...) the expression of neural proteins (e.g. eNCAM, MAP II, beta-tubulin, nestin, NF, and NF-PO4, vimentin, Sox2, Ki-67, GD2 ganglioside, MAP2ab, NeuN, FMRP, Tau, GFAP, dublecortin, CD133, CD44, CD81, CD90, CD29, NumA and etc...) or the treatment of complex neurodegenerative conditions (e.g., multiple sclerosis, Alzheimer's disease, Parkinson's disease, amyotrophic lateral sclerosis, Huntington's chorea, diabetes, sinile dementia, dysplasia, myelitis, spinal ataxia, Friedreich's ataxia, cerebellar cortical degenerations, Refsum's disease, abetalipoprotemia, ataxia, telangiectasia, mitochondrial multi.system disorder, transverse myelitis, anterior horn cell degeneration, such as amyotrophic lateral sclerosis, infantile spinal muscular atrophy and juvenile spinal muscular atrophy, Down's Syndrome in middle age, Diffuse Lewy body disease, Wernicke-Korsakoff syndrome, chronic alcoholism; Creutzfeldt-Jakob disease, Subacute sclerosing panencephalitis, Hallerrorden-Spatz disease, Dementia pugilistica, etc...), that are known today, and those that may be discovered in the future.

For the reasons given above, in view of the nature of the invention, the amount of guidance present in the specification, the breadth of the claims, the relative skill of those in the art, and the predictability or unpredictability of the art, the Examiner alleges that it would take undue trials and errors to practice the invention as claimed.

Applicants respectfully traverse the Examiner's rejection and have amended the claims to better clarify aspects of the invention.

More particularly, Applicants have amended claim 8 to recite:

"A method for promoting growth or differentiation of neural precursor cells *in vitro,* wherein said cells express at least one protein selected from the group consisting of eNCAM, MAP II, β-tubulin, nestin, NF and NF-PO_4, comprising exposing said cells to a neural precursor growth or differentiation promoting effective amount of a composition containing a compound..."

Support for this amendment and for enablement of this aspect of the invention, as now claimed, can be found in Examples 1 and 2, found on pages 41-45, and in Example 4 on pages 50-52. The results of these experiments, as depicted in photographs of the cell cultures, were provided to the Examiner with a Declaration under 37 C.F.R. §1.132 signed by Dr. Timothy Neuberger, and forwarded with the response to the last Office Action, dated November 5, 2004.

Furthermore, claim 19 has been amended to recite:

"A method for promoting growth or differentiation of neural precursor cells *in vitro* after injury to the neuronal cells, wherein said neural precursor cells express at least one protein selected from the group consisting of eNCAM, MAP II, β-tubulin, nestin, NF and NF-PO_4, the method comprising exposing said cells to an effective amount of a composition containing ....."

Support for this amendment and for enablement of this aspect of the invention, as now claimed, can be found in Example 1 on pages 41-43 of the instant application. More particularly, the disclosure on page 41, lines 26-30, continuing onto page 42, lines 1-12 delineates the actual experimental protocol with glutamate. The immunostaining procedure using the antibodies specific for the neural precursor cell proteins, as currently claimed, is found on page 42, lines 13-30, continuing onto page 43, lines 1-13. As noted in the specification, the neural precursor cells obtained from the brains of embryonic rat pups were allowed to mature in culture for 10 days, at which time it is known to those skilled in the art that glutamate receptors are expressed on these mature neuronal cells.

These cells are then injured by exposing the cells to glutamate, followed by incubation in the presence or absence of a compound of the present invention. After the specified time in culture, the cells were stained using antibodies specific for certain proteins (as currently claimed) that are characteristic of neural precursor cells as outlined in the specification. Further support for injury to neuronal is found in Example 3, whereby the neuronal cells are injured using a spinal cord contusion model.

In addition, claim 34 has been amended to recite:

"A method for promoting growth or differentiation of neural precursor cells, said cells expressing at least one protein selected from the group consisting of eNCAM, MAP II, β-tubulin, nestin, NF and NF-PO_4, comprising administering to a first mammal a neural precursor cell growth or differentiation promoting effective amount of a composition, collecting bone marrow cells from the first mammal and delivering them to a site of injury in the first mammal or in a second mammal; wherein the composition comprises a compound ..."

Support for the claim amendment and for enablement of this aspect of the invention, as now claimed, can be found in Example 3 on pages 45-50.

Furthermore, claim 46 has been amended to recite:

"A method for treating an injury to neuronal cells, said cells expressing at least one protein selected from the group consisting of MAP II, β-tubulin, NF and NF-PO_4, comprising exposing said cells to an effective amount of a composition containing a compound ..."

Support for this amendment and for enablement of this aspect of the invention, as now claimed, can be found in Example 1 on pages 41-43 of the instant application. More particularly, the disclosure on page 41, lines 26-30, continuing onto page 42, lines 1-12 delineates the actual experimental protocol with glutamate. The immunostaining procedure using the antibodies specific for the neural precursor cell proteins, as currently claimed, is found on page 42, lines 13-30, continuing onto page 43, lines 1-13. As noted in the specification, the neural precursor cells obtained from the brains of embryonic rat pups were injured by exposing the cells to glutamate, followed by incubation in the

presence or absence of a compound of the present invention. After the specified time in culture, the cells were stained using antibodies specific for certain proteins (as currently claimed) that are characteristic of neural precursor cells as outlined in the specification.

In addition, claim 55 has been amended to recite:

"A method for increasing the number of neural precursor cells expressing at least one protein selected from the group consisting of eNCAM and nestin, comprising contacting said cells with an effective amount of a composition containing a compound ..."

Support for this claim amendment and for enablement of this aspect of the invention can be found particularly in Examples 1 through 4 on pages 41- 52.

Furthermore, claim 57 has been amended to recite:

"A method for promoting growth and differentiation of neural precursor cells in a mammal in need of such therapy, comprising

(a) administering a population of neural precursor cells obtained from a first mammal treated with a compound having one of the following structural formulas .....

b) collecting neural precursor cells expressing at least one protein selected from the group consisting of eNCAM, MAP II, β-tubulin, nestin, NF and NF-PO_4, from said first mammal and delivering said cells to a site of injury in the first mammal or to a site of injury in a second mammal in need of such therapy."

Support for this claim amendment and for enablement of this aspect of the invention, as now claimed, can be found particularly in Example 3 on pages 45-50.

As noted above, the Examiner alleges that it would take undue experimentation for one skilled in the art to practice the invention, given the original scope of the claims. Applicants respectfully traverse the Examiner's assertion and have amended the claims as noted above to better clarify the invention. Based on these amendments, and on the support provided in the instant specification for enablement of these aspects of the invention, Applicants assert that it would not take undue experimentation for a skilled practitioner to practice the invention as currently claimed.

Accordingly, withdrawal of the rejection is respectfully requested.

Rejections Under 35 USC § 102(b)

Claims 8-12, 19-23, 57, 67 and 69-72 are rejected under 35 USC 102(b) as being anticipated by Nair, *et al.* (US 4965284).

The Examiner alleges that Nair teaches the use of the claimed compounds for modulating the immune system; stimulating the proliferation and differentiation of blood cell progenitors in bone marrow of warm-blooded animals (ultimately for human); accelerating the recovery of white blood cell progenitors in bone marrow of warm-blooded animals; and enhancing the activity of immune cells and/or immunoregulatory proteins, wherein said compound is administered to warm-blood animal or warm-blood animals conditioned to chemical or irradiation therapy in amounts ranging from about 5 mg to about 400 mg/kg of body weight per day, preferably from about 25 mg to about 500 mg/kg of body weight per day (column 8, lines para. 1; column 12, lines 60-66; claims, especially claims 16-23).

Furthermore, the Examiner notes that although Nair is silent about the instantly required "promoting neural tissue regeneration or expression" (claim 8); "the tissue is of neuronal origin and the method is for promoting neural expression" (claim 10); "the administration is effective to promote the neural expression of one or more proteins selected from the group consisting of: eNCAM, MAP II, beta-tubulin, nestin, NF, and NF-PO4" (claim 12); "promoting recovery of behavioral function of neurons after a decrease in neural function" (claim 19); and "promoting regeneration of neural precursor cells" (claim 57), such properties or characteristic deem to be inherently presented in the referenced method. The Examiner alleges that where the administration of same compound (i.e., N-[4-[(4-fluorophenyl) sulfonyl]phenyl]-acetamide) at overlapping dosage amounts (i.e. about 5 mg to about400 mg/kg of body weight per day, preferably from about 25 mg to about 500 mg/kg of body weight per day) to same treatment population (i.e., "warm blooded animal", "warm blooded animal" conditioned to "chemical or irradiation therapy"), the instantly claimed mechanism of action must be inherently presented in the prior art (Nair). Therefore, the Examiner alleges that Nair anticipates the claimed invention.

Applicants respectfully traverse the Examiner's rejection for the following reasons. The present application teaches methods for promoting growth or differentiation

of neural precursor cells comprising exposing said cells to a composition containing a compound selected from a genus of compounds, wherein said contacting is effective to promote the growth or differentiation of neural precursor cells. Furthermore, these neural precursor cells are identified on the basis of expression of one or more proteins selected from the group consisting of : eNCAM, MAP II, β-tubulin, nestin, NF and NF-PO_4. In addition, the present application teaches methods for promoting the growth or differentiation of neural precursor cells expressing neuronal cell markers after injury to the neuronal cells through use of a compound from this genus. The instant application further teaches a method for promoting growth or differentiation of neural precursor cells comprising administering to a first mammal a neural growth or differentiation promoting effective amount of a composition, collecting bone marrow cells from the first mammal and delivering them to a site of injury in the first mammal or in a second mammal; wherein the composition comprises the compound from the genus described. Furthermore, the administering is effective to promote the expression of one or more proteins selected from the group consisting of : eNCAM, MAP II, β-tubulin, nestin, NF and NF-PO_4. The present application further teaches a method for treating injury to neuronal cells comprising exposing said cells to an effective amount of a composition containing one of the compounds of the genus described, wherein said administering is effective to promote the neuronal cell expression of one or more proteins selected from the group consisting of : eNCAM, MAP II, β-tubulin, nestin, NF and NF-PO_4. The injury to neuronal cells may be the result of surgery, radiation therapy, chemotherapy or excititoxic agents.

Moreover, claims 8 and 19 have been amended to recite:

"A method for promoting growth or differentiation of neural precursor cells ***in vitro*** ...."

In addition, claim 57 has been amended as follows:

"A method for promoting growth and differentiation of neural precursor cells in a mammal in need of such therapy, comprising

(a) administering a population of neural precursor cells obtained from a first mammal treated with a compound having one of the following structural formulas .....

b) collecting neural precursor cells expressing at least one or more proteins selected from the group consisting of eNCAM, MAP II, β-tubulin, nestin, NF and NF-PO_4, from said first mammal and delivering said cells to a site of injury in the first mammal or to a site of injury in a second mammal in need of such therapy."

Nair et al. teach the use of the claimed compounds for modulating the immune system and for stimulating the proliferation and differentiation of blood cell progenitors, and for enhancing the activity of immune cells and/or immunoregulatory proteins ***in vivo***. The Examiner asserts that Nair et al is silent with respect to "the tissue is of neuronal origin and the method is for promoting neural expression"; "the administration is effective to promote the neural expression of one or more proteins selected from the group consisting of eNCAM, MAP II, beta tubulin, nestin, NF and NF-PO4"; Promoting recovery of behavioral function of neurons after a decrease in neural function" and "promoting regeneration of neural precursor cells". However, the Examiner alleges that these properties are deemed to be inherently presented in the Nair reference.

Applicants respectfully traverse the Examiner's rejection and assert that in order for a rejection under 35 U.S.C. 102(b) to be proper, the reference(s) must recite each and every element of the invention as claimed. Applicants assert that Nair et al. do not teach the ***in vitro*** methods of the present invention as currently claimed **or the methods for neural precursor cell transplant from a donor animal to a recipient, as currently claimed**. Applicants assert that there are distinct differences between the teachings of Nair et al. and the presently claimed invention.

For example, Nair et al. **do not teach or suggest** the use of this genus of compounds for growth or differentiation of neural precursor cells ***in vitro***. Furthermore, Nair et al. **do not teach or suggest** that this genus of compounds could be used to treat neural precursor cells obtained from **neural tissue** or non-neural tissue to result in growth or differentiation of a population of neural precursor cells ***in vitro,*** which express proteins characteristic of neuronal precursor cells. Moreover, Nair et al. **do not teach or suggest** the use of this genus of compounds for treating injury to neural precursor cells ***in vitro***.

Nair et al. provide no teaching as to how one can obtain neural tissue for treatment with the compounds of this genus. Nor do Nair et al. **teach or suggest** how one can utilize the neural stem cells or precursor cells obtained from the bone marrow or from neural tissue to treat a mammal that has experienced an injury to nervous system tissue, for example, a contusion to the spinal cord.

Accordingly, Applicants assert that Nair et al. **do not** anticipate the present invention as currently claimed. Nair et al. do not teach or suggest the methods of the current invention for treating injury to neural cells by stimulating growth and differentiation of **neural stem cells or precursor cells**, nor do Nair et al. provide enablement as to how one may utilize these compounds for treating injury to neuronal cells or tissue. Nair et al. only teach the use of this genus of compounds for treating disorders in which the **hematopoietic** stem cell system is compromised, such as in cancer patients whereby the chemotherapy or irradiation therapy destroys **hematopoietic stem cells**, thus leading to a decrease in peripheral blood cell counts, resulting in neutropenia and susceptibility to infections following such therapies.

Applicants further assert that the rejection under 35 U.S.C. § 102(b) is improper in that the Nair et al reference is a non-enabling reference. As stated in In re Donohue, 766 F.2d 531, 533, 226 USPQ 619, 621 (Fed. Cir. 1985):

> It is well settled that prior art under 35 U.S.C. § 102(b) must sufficiently describe the claimed invention to have placed the public in possession of it. Accordingly, even if the claimed invention is disclosed in a printed publication, that disclosure will not suffice as prior art if it was not enabling. It is not, however, necessary that an invention disclosed in a publication shall have actually been made in order to satisfy the enablement requirement.

For example, Applicants assert that Nair et al. do not teach or suggest the use of the compound of the present invention for promoting the growth or differentiation of neural precursor cells ***in vitro***, as currently claimed. As noted by the Examiner, Nair et al. specifically teaches the use of the claimed compounds for "modulating the immune system; stimulating the proliferation and differentiation of blood cell progenitors in bone marrow of **warm-blooded animals**". Furthermore, as also noted by the Examiner, Nair et al teach that **the compounds are administered to warm-blood animal or warm-blood animals** conditioned to chemical or irradiation therapy in amounts ranging from about 5 mg

to about 400 mg/kg of body weight per day, preferably from about 25 mg to about 500 mg/kg of body weight per day (column 8, lines para. 1; column 12, lines 60-66; claims, especially claims 16-23). Applicants assert that Nair et al. are silent as to the use of the compounds of the present invention for promoting the growth or differentiation of neural precursor cells ***in vitro.***

In addition, Nair et al. **do not teach or suggest** the use of the compounds of the present invention **for the transplant of neural precursor cells from a treated animal to a recipient (untreated) animal in need of such therapy**, such as in an animal suffering from an injury to nervous tissue, such as, but not limited to, a spinal cord injury.

Furthermore, Applicants assert that certain conditions must be met before an element may be found to be inherent in the disclosure of a prior art reference. These conditions (as settled by the Federal Circuit citing the review article of Feit et al. (2003, J. Pat. Trade Off. Soc., Vol. 85, No. 1, pages 5-21) are as follows:

1. Certainty. The prior art reference must ***necessarily*** and ***certainly*** result in the invention as claimed including the elements of the claimed invention that are not expressly disclosed by the reference.

2. Chronology. The prior art reference must ***always*** result in the invention as claimed including the elements of the claimed invention that are not expressly disclosed by the reference.

3. Recognition. One of ordinary skill must ***recognize*** that the elements of the claimed invention that are not expressly disclosed by the reference are present in the disclosure of the prior art reference.

Applicants assert that Nair et al. do not meet a single of these three criteria as required by the law. Applicants respectfully point out to the Examiner that Nair et al. do not teach or suggest all of the limitations of claims 8-12, 19-23, 57, 67, and 69-72 as currently amended, either expressly or inherently.

In light of the foregoing claim amendments and arguments, Applicants respectfully request withdrawal of the rejection. It is to be understood that the claims have been amended solely to place the application in condition for allowance. Applicant reserves the right to pursue the remaining subject matter in further Divisional applications.

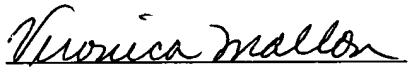
Fees

A check in the amount of $60. is enclosed to cover the Petition for a one month extension of time. No other fees are believed to be necessitated by the present response. However, should this be in error, the Commissioner is hereby authorized to charge any fees, or credit any overpayment, to Deposit Account No. 11-1153.

Conclusion

Applicants believe that the foregoing amendments to the claims place the application in condition for allowance. Withdrawal of the rejections and objections is respectfully requested. If a discussion with the undersigned will be of assistance in resolving any remaining issues, the Examiner is invited to telephone the undersigned at (201) 487-5800, ext. 118, to effect a resolution.

Respectfully submitted,



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